IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

ATTY.'S DOCKET: KORSGREN=1

In re Application of:	)	Art Unit: 1614
	)	
Olle KORSGREN et al	)	Examiner: Donna JAGOE
	)	
Appln. No.: 09/890,936	)	Washington, D.C.
	)	
Date Filed: November 7, 2001	)	Confirmation No. 9165
	)	
For: NOVEL USE WITHIN TRANSPLANTATION SURGERY	)	

DECLARATION UNDER 37 CFR 1.132

Olle Korsgren, Bo Nilsson and Rolf Larsson hereby each solemnly declare as follows:

We are co-applicants and co-inventors of the above-identified application. We each have Ph.D. degrees and Korsgren and Nilsson also have M.D. degrees. Our CVs are attached hereto and made a part of this declaration.

Each of us is an expert in the art of the present application, and each of us is familiar with the prior art documents cited and relied upon by the U.S. patent examiner and the commentary of the U.S. examiner in conjunction with the examiner's reliance on these prior art citations.

First, and in a general way, we can state as fact that our invention as set forth in the present application is not based on the same principles, i.e. encapsulation, as the Wagner et al citation DE 196 23 440 A 1 (hereinafter "Wagner")

or the Soon-Shiong et al citation U.S. patent 5,705,270 (hereinafter "Soon-Shiong"). We elaborate below.

The U.S. examiner has stated (Advisory Action), "Coating and encapsulating appear to be the same." And that, "this appears to be a difference in nomenclature only." We state as fact that coating according to our invention is absolutely not the same as encapsulating according to Wagner and Soon-Shiong. Coating in accordance with our invention of the present U.S. Patent application does not result in encapsulation, but instead results in a linkage between the islets and the heparin or other clotting preventing agent, i.e. the "coating" according to our invention results in the isolated islets being modified by irreversible adsorption with the heparin, a physical condition which is entirely unlike encapsulation with a polymeric material as disclosed by Wagner and Soon-Shiong.

Fabrication of microcapsules surrounding individual or small clusters of islets (encapsulation) as represented by Wagner and Soon-Shiong represents a very delicate process. The procedure consists of enveloping the islets cells within homogeneous and semi-permeable artificial membranes without affecting tissue morphologic integrity or functional competence, aiming at protecting the graft from rejection in the absence of immunosuppressive therapy. Thus, the membrane

should be permeable to insulin and low molecular weight components such as oxygen, glucose, electrolytes and other nutrients and impermeable to lymphocytes and other cellular components of the immune system and also to antibodies, cytokines and other mediators of the immune system.

Such microcapsules, including those produced according to the methods of Wagner and Soon-Shiong, consist of polymer spheres of 400-800 µm in diameter, typically made of alginate (a polysaccharide) or synthetic polymers, with a wall thickness of 10-50 µm, or even more, to separate the encapsulated islets from their biological environment, the ultimate goal of the capsule shell being to establish an immunological barrier. Encapsulation implies a coherent material in the form of a sphere which is not integrated into the biological surface of the islets but rather holds a number of islets being dispersed in the interior of the spheres.

From a technical standpoint, a rather elaborate, semi-automatic procedure is required. It would be very clear for those skilled in the art that the procedures according to the present patent application are much less complicated from a technical point of view.

The references of Wagner and Soon-Shiong therefore are very clearly concerned with encapsulation techniques, very different from our technique. As an example, both references

teach the use of alginate as a vehicle to construct microcapsules. The encapsulation techniques according to Wagner and Soon-Shiong result, according to what is desired and clearly implied in these documents, in the islets being trapped and physically enclosed within the microspheres, i.e. within the capsule shells. As indicated above, this is a physical state which is quite different from what occurs according to our method.

It is well known that the main reason for using encapsulation is to avoid immunological reactions aiming at eliminating the need for immunosuppressive therapy. However, despite great efforts over two decades, there is still no encapsulation method in clinical practice, which reflects the practical and biological difficulties related to this prior approach.

The approach according to the present patent application is to rely on well-established protocols for immunosuppression, but to improve the viability of islets being injected in the portal vein of diabetic patients. There is no aim whatsoever to create an immunological barrier, as with encapsulation, but to down-regulate the inherent pro-coagulant and pro-inflammatory capacity of isolated islets. Recent research has taught us that isolated islets display a pronounced pro-coagulant and pro-inflammatory capacity which

provokes an instant blood mediated inflammatory response (IBMIR), which is distinctly different from a specific immunogenic challenge, i.e. the type of immune response triggered by transplanted cells or organs. The IBMIR leads to blood clot formation (thrombosis) which implies that a great number of islets become trapped in such thrombi and thus become non-functional.

In the case where the islets have been modified by e.g. the Corline Heparin surface (e.g. our Example 3), there are no prerequisites that would lead anyone skilled in the art to conclude that such a procedure involving simple mixing would represent encapsulation. The procedure implies (and results in) attachment to the biological structure of the islets of individual high-molecular weight molecules, with no semi-permeable function.

The U.S. Examiner has questioned what is meant by "artificial" encapsulation, and how our invention differs. We have in part addressed this above, and now add that what is "artificial" in Wagner and Soon-Shiong is the creation of an artificial shell of polymeric material, i.e. the capsule which encapsulates whatever component is intended to be encapsulated. In our invention, contrary to Wagner and Soon-Shiong, no such capsule is formed. The heparin in our invention does not encapsulate the islets. Even when a

heparin-conjugate composed of multiple heparin molecules being covalently linked to a carrier chain, e.g. the Corline heparin conjugate of Example 3 of our above-identified U.S. Patent application, is used, encapsulation of the islets does not occur.

We summarize differences between encapsulation, e.g. according to Wagner and Soon-Shiong, and heparin coating of islets according to the present invention as follows:

We state as fact that it is inherent in our above-identified U.S. patent application that the surface of each individual islet is modified to reduce thrombogenicity, and each islet is free to interact with the biological environment. No physical barrier and no immunological barrier occur in our invention. On a molecular level there is provided a thickness of heparin of at most 0.1 μm, which is non-coherently attached directly to the biological surface of the islets.

Artificial encapsulation implies that a synthetic polymer is used to establish a physical barrier between the islets and the biological environment (tissue, blood, etc.) only to allow certain substances (e.g. insulin) to pass across the barrier. Our process of the present application may be referred to as non-artificial based on the fact that the islets are free to fully interact at a molecular scale with

their biological environment and that they retain their capacity to release insulin without any passage through a semi-permeable membrane. The purpose of attaching e.g. heparin to the surface of the islets is entirely to down-regulate the tendency of the islets to induce coagulation and inflammation.

We therefore state as fact that our islets, after "coating" with heparin, are not encapsulated.

Our heparin-modified islets can be obtained by simple mixing of heparin or heparin complex with the islets, as in Example 3 of our U.S. patent application. On the other hand, in Wagner and Soon-Shiong there are required operations, which are the main focus of these documents, for the creation of the capsule shells, e.g. extrusion in a two-phase coaxial flow system according to Example 20 of Soon-Shiong, or an emulsification technique with a photo polymerization as set forth in Example 19 of Soon-Shiong.

The third citation relied upon by the U.S. examiner is a publication in the name of Lenschow et al. This publication is in certain respects even more remote from our invention than are Wagner and Soon-Shiong, because the authors simply administered CTLA4Ig to mice rather than treating the islets, i.e. the CTLA4Ig was administered systemically to the

mice and not to the islets. The Lenschow et al publication therefore has nothing to do with our invention.

I hereby further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 2004-02-24 By _____
Olle Korsgren

Date: 2004-02-23 By _____
Bo Nilsson

Date: 2004-02-23 By _____
Rolf Larsson

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Applicant: Olle Korsgren

Curriculum vitae

Biografical sketch:

Name: Olle Korsgren

Date and place of birth: June 19, 1959, Falun, Sweden

Social security number: 590619 7214

Family: married, 6 children

Home address: Tallmovägen 2A, S-756 45 Uppsala, Sweden

Education:

Uppsala university, Uppsala, Sweden	Bachelor of Medicine	1982
Uppsala university, Uppsala, Sweden	M.D.	1986
Uppsala university, Uppsala, Sweden	Ph. D.	1991
Uppsala university, Uppsala, Sweden	Assist. Prof.	1994
National Board of Health and Welfare	License to practice Medicine	1994
National Board of Health and Welfare	Specialist in Clinical Immunology	2001

During my period as a medical student, 1982-1986, I attended several different university courses, corresponding to 68 weeks of full-time studies.

Research and professional experience:

Positions held:

1986-1988	Ph.D. Student	Fellowship, Uppsala University
1988-1991	Ph.D. Student	Fellowship, Swedish Medical Research Council
1991	Postdoc Research	Fellowship, Uppsala University
1992-1994	Intern	Uppsala University Hospital
1994-2000	Resident	Clinical Immunology, Uppsala University Hospital
1996-2000	Research Career Award	Swedish Medical Research Council
2001-	Senior Research position, (6 years, halftime) Swedish Medical Research Council	
2001-	Senior staff member Dept of Clinical Immunology, University Hospital, Uppsala	
2002-	Professor of Transplantation Immunology, Uppsala university	

Administrative experience:

1986-1991	Member of the Medical Faculty Board, Uppsala University
1989-1991	Member of the Board, Dept. of Medical Cell Biology
1997-1998	Member of the Board, Dept. of Clinical Immunology
1998-2000	Member of the Board, Swedish Transplantation Society
1999-	Member of the Editorial board Xenotransplantation
1999-	Member of the Editorial board Transplantation

Nilsson, SI Bo **MD, PhD**

Degrees

B. of Med.	1976	Uppsala university, Sweden
M.D.	1986	Uppsala university
Ph.D.	1986	Exp Clin Chemistry, Uppsala university,
Assist. Prof (Docent)	1990	Exp Clin Chemistry Uppsala university
Specialist	1991	Clinical Immunology, University Hospital, Uppsala

Society Memberships

Member of the Scandinavian Society of Immunology
Member of the Swedish Medical Society
Member of the International Complement Society

Awards and stipends

Clinical research stipend	1994-2003	Total 30 month
Novo nordisk Research stipend	2000-2003	Total 18 month (3 x 6 month)

Positions held:

1980-1986	Ph.D. Student	Fellowship, Uppsala University
1987-1988	Internship	University Hospital, Uppsala
1989-1991	Residency	University Hospital, Uppsala
1992-1993	Registrar	University Hospital, Uppsala
1993-	Chief Physician	University Hospital, Uppsala

Administrative experience:

1992-1995	Member of the Board, Dept. of Clin Laboratories
1994-	Member of the Board, Dept. of Clinical Immunology
1998-	Member of the Board of External quality assurance in laboratory medicine in Sweden (in clinical immunology)
1999-	Treasurer, Swedish Clinical Immunology Society
1999-	Member of the Board of the Swedish Expert group for Clinical Immunology
1999-2001	Head of the autoimmune immunochemistry unit, Dept Clin immunol, University Hospital, Uppsala

Relevant Publications (selected out of 116)

1. Bennet W, Sundberg B, Groth CG, Brendel MD, Brandhorst D, Brandhorst H, Bretzel RG, Elgue G, Larsson R, Nilsson B, Korsgren O. Incompatibility between human blood and isolated islets of Langerhans: a finding with implications for clinical intraportal islet transplantation? Diabetes 1999;48(10):1907-1914.
2. Özmen, L., Nilsson Ekdahl, K., Elgue, G., Larsson, L., Korsgren, O., Nilsson, B (2002). Inhibition of thrombin with Melagatran abrogates instant blood mediated islet reaction (IBMIR) in vitro: Possible application in clinical allogeneic islet transplantation. Diabetes 51 (6):
3. Moberg, L., Lukinius, A., Johansson, H., Elgue, G., Nilsson Ekdahl, K., Korsgren, O., Nilsson, B. (2002) Expression and secretion of tissue factor in the islets of Langerhans: A likely explanation for the development of the thrombotic reactions in clinical islet transplantation. Lancet Dec 21-28;360(9350):2039-45
4. Johansson U, Olsson A, Gabrielsson S, Nilsson B, Korsgren O. Cytokines and cytokine receptors cDNA array analyses of isolated human islets. Biochem Biophys Res Commun 2003;29:474-479.

Curriculum vitae

Rolf Larsson (460128-5531)

Education and academic degrees

1972 Chalmers University of Technology, Gothenburg, Sweden. M. Sci in Chemical Engineering

1980 Karolinska Institute, Dept of Experimental Surgery, Stockholm, Sweden. by the thesis " Chemical constitution and biological characteristics of a heparin surface".

1994 Uppsala university, Dept of Clinical Immunology, Uppsala, Sweden. Associate Professor in Experimental Biomaterials Research

1996 Uppsala university, Dept of Clinical Immunology, Uppsala, Sweden. Adjunct Professor in Experimental Biomaterials Research

Positions held:

1996 -	Senior Research Position	University Hospital, Uppsala
1991 -	Research Director	Corline Systems AB, Uppsala, Sweden
1984 – 1991	Research Scientist	Pharmacia AB, Uppsala, Sweden
1972 – 1984	Research engingeer	Incentive Research & Development AB

Present position

1. Adj. Prof. Experimental Biomaterials Reseach, Dept of Oncology, Radiology and Clinical Immunology, Uppsala University since 1996. Assignment 40%.
2. Research Director of Corline Systems AB (permanent position).

Bibliography, last 4 years

Dissertations which have involved supervision

1. Jaan Hong Investigation of Incompatibility Reactions Caused by Biomaterials in Contact with Whole Blood Using a New in vitro Model. Dissertation Uppsala University. 2001

2. Jonas Andersson. Complement Activation Triggered by Biomaterial Surfaces. Dissertation Uppsala University. 2003.

3. Matilda Johnell. Monocytes, Tissue Factor and Heparin-coated Surfaces. Clinical and Experimental Studies. Dissertation Uppsala University. 2003.

Original papers

1 Hong, J., Nilsson Ekdahl, K., Reynolds, H.,. Larsson, R., Nilsson, B. A new in vitro model to study interaction between whole blood and biomaterials. Studies of platelet and coagulation activation and the effect of aspirin (1999) Biomaterials (1999) 20: 603-11.

2 Hong, J., Larsson, A., Nilsson Ekdahl, K., Elgue, G., Larsson, R, and Nilsson, B.: Contact between a polymer and whole blood: The sequence of events leading to thrombin generation. J. Lab. Clin. Med. 2001, 138, 139-45

3 Hong J, Andersson J, Nilsson Ekdahl K, Elgue G, Axén N, Larsson R and Nilsson B: Titanium is a highly thrombogenic biomaterial: Possible implications for osteoneogenesis. (1999) Thromb. Haemostas. 82:58-64

4 Nilsson, B., Hong, J., Larsson, R., Elgue, G., Nilsson Ekdahl, K., Sahu, A, & Lambris, J. D. Compstatin inhibits complement and cellular activation in whole blood in models for extracorpereal circulation (1998) Blood 92: 1661-1667.

Review papers

1. van der Giessen, W.; van Beusekom, H.M.M.; Larsson, R.; Serruys, P.W. Heparin-coated Coronary Stents. Curr. Interventional Cardiol. Reports. 1999. 1, 234-40.

2. Larsson, R.: Heparin-binding to improve biocompatibility. In Encyclopedia for Biomaterials and Bioengineering. Marcel Dekker Inc. 2003, In press.